United States Court of Appeals for the Federal Circuit

2006-1530, -1555

AVENTIS PHARMA DEUTSCHLAND GMBH,

Plaintiff-Cross Appellant,

and

KING PHARMACEUTICALS, INC.,

Plaintiff-Cross Appellant,

v.

LUPIN, LTD.
and LUPIN PHARMACEUTICALS, INC.,

Defendants-Appellants.

Joel Katcoff, Kaye Scholer LLP, of New York, New York, argued for plaintiff-cross appellant Aventis Pharma Deutschland GmbH. With him on the brief were Benjamin C. Hsing, Sapna Walter Palla, and Tatiana N. Alyonycheva.

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Deanne M. Mazzochi, Rakoczy Molino Mazzochi Siwik LLP, of Chicago, Illinois, argued for defendants-appellants. With her on the brief were William A. Rakoczy, Paul J. Molino, and Alice L. Riechers.

Appealed from: United States District Court for the Eastern District of Virginia

Judge Robert G. Doumar

United States Court of Appeals for the Federal Circuit

2006-1530, -1555

AVENTIS PHARMA DEUTSCHLAND GMBH,

Plaintiff-Cross Appellant,

and

KING PHARMACEUTICALS, INC.,

Plaintiff-Cross Appellant,

v.

LUPIN, LTD. and LUPIN PHARMACEUTICALS, INC.,

Defendants-Appellants.

DECIDED: September 11, 2007

Before MAYER and LINN, Circuit Judges, and ROBERTSON, District Judge.[*]

LINN, Circuit Judge.

This is a patent infringement action concerning the pharmaceutical compound ramipril, which is marketed by King Pharmaceuticals, Inc. ("King") as a blood pressure medication under the name Altace®. Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") appeal from a final judgment of infringement entered by the United States District Court for the Eastern District of Virginia in favor of King and Aventis Pharma Deutschland GmbH ("Aventis"). Aventis Pharma Deutschland GmbH v. Lupin Ltd., No. 2:05-CV-421 (E.D. Va. July 18, 2006). The district court concluded at

[*] Hon. James Robertson, District Judge, United States District Court for the District of Columbia, sitting by designation.

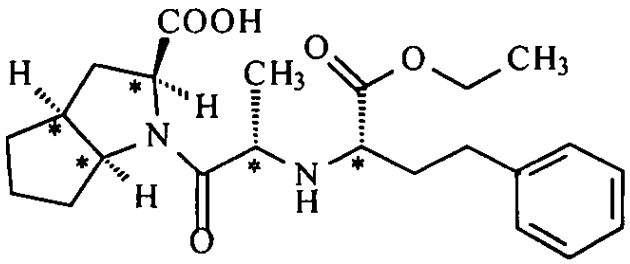
summary judgment that Lupin's filing of an Abbreviated New Drug Application (ANDA) for a generic version of ramipril infringed Aventis's U.S. Patent. No. 5,061,722 ("the '722 patent") under the doctrine of equivalents, and concluded after a bench trial that the asserted claims of the '722 patent were not invalid.[1] Lupin appeals from these decisions. Aventis cross-appeals from the district court's decision to dismiss its claim of willful infringement. For the reasons that follow, we conclude that the subject matter of the asserted claims of the '722 patent would have been obvious. Accordingly, we reverse. The cross-appeal and the remaining issues raised by the parties are deemed moot and are not addressed.

I. BACKGROUND

A. The Claimed Technology

The patent at issue in this appeal is directed to the pharmaceutical compound ramipril in a formulation "substantially free of other isomers." Ramipril, like many complex organic molecules, is one of a family of stereoisomers. As the district court explained in greater detail in its opinion regarding validity, Aventis Pharma Deutschland GmbH v. King Pharms., Inc., No. 2:05-CV-421 (E.D. Va. July 17, 2006) ("Invalidity Opinion"), an isomer of a compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but with those atoms arranged differently. A stereoisomer is an isomer in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. The following structural formula represents ramipril:

[1] Aventis is the owner of the '722 patent, and King is its exclusive licensee. Both parties are plaintiff-cross appellants. For convenience, and because Aventis and King have adopted each other's arguments on appeal pursuant to Fed. R. App. P. 28(i), we refer to them collectively as "Aventis."



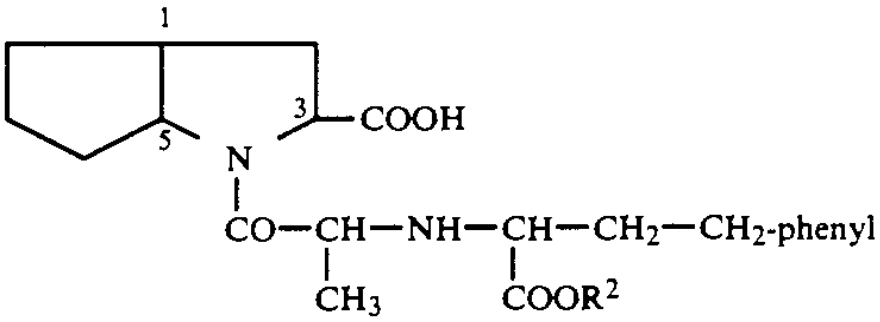
Each of the five carbon atoms marked with an asterisk can be spatially oriented in two different ways.[2] For example, the dashed triangle leading from the leftmost marked carbon to a hydrogen ("H") atom indicates that the hydrogen atom lies below the planes of the two five-sided rings of which the carbon atom is a part. The hydrogen atom may also lie above the planes of the rings, resulting in a structure that is a stereoisomer of ramipril. Because there are five carbon atoms that may take either of two orientations—or five "stereocenters," as such atoms are known—ramipril is one of 2^5, or 32, stereoisomers. There are a number of different ways of naming these stereoisomers; one comparatively simple system, used by both parties and by the district court, involves labeling each stereocenter with an "R" or an "S" depending on its configuration. Using this system, all five stereocenters in ramipril are in the "S" configuration, so it is known as an "SSSSS" or "5(S)" stereoisomer. Other stereoisomers would include RRRRR, SSSSR, RRSSS, etc.

Some of the prior art references also use the terms "enantiomer" and "diastereomer." Enantiomers are stereoisomers that are mirror images of each other, like left and right hands. Diastereomers are stereoisomers that are not enantiomers.

[2] As is customary in chemical diagrams, carbon atoms may be indicated by an intersection of two line segments; in such cases, hydrogen atoms that are bonded to the carbons may be omitted from the diagram for simplicity and should be inferred.

The asserted claims of the '722 patent read as follows:

1. A compound of the formula



or a physiologically acceptable salt thereof, wherein R^2 is hydrogen, methyl, ethyl, or benzyl, and wherein hydrogen atoms on the ring carbon atoms in the 1- and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3-position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration, said compound or salt being substantially free of other isomers.

2. A compound or salt as in claim 1 which is N-(1-S-carboethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid or a salt thereof.

4. A hypotensive composition for reducing blood pressure comprising a hypotensively effective amount of a compound or salt as in claim 1 and a pharmaceutically acceptable excipient therefor.

5. A method for reducing blood pressure in a patient which comprises administering to said patient a hypotensively effective amount of a compound or salt as in claim 1.

Claim 1, the only independent claim, covers a small genus of compounds, each of which has a different functional group at location R^2. The language of the claim, "wherein hydrogen atoms on the ring carbon atoms in the 1- and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3-position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration," limits claim 1 (and thus all the other claims) to the 5(S) stereoisomer.

When the R^2 functional group is ethyl, the compound of claim 1 is ramipril. This is the compound claimed specifically by claim 2.

B. The Development of Ramipril

Ramipril is one of a family of drugs known as "Angiotensin-Converting Enzyme inhibitors," or "ACE inhibitors." ACE inhibitors inhibit a biochemical pathway that constricts blood vessels and therefore are useful for treating high blood pressure. The earliest ACE inhibitors, dating back to the late 1960s, were based on the venom of the Brazilian Viper, which was known to reduce blood pressure. The active compound isolated from viper venom, known as BPP_{5a}, has six stereocenters, all of which are in the S configuration. Synthetic ACE inhibitors have been developed by making structural modifications to this venom and to successive generations of ACE inhibitors. For example, captopril, the first synthetic ACE inhibitor, consists of part of the BPP_{5a} molecule with a sulfur atom at the end. Captopril retains two stereocenters from BPP_{5a}, both of which remain in the S configuration.

Ramipril's immediate predecessor is an ACE inhibitor known as enalapril that was introduced by Merck in 1980. Enalapril has three stereocenters. In a published article, Merck scientists explained that the all-S (SSS) stereoisomer of enalapril was found to have 700 times the potency of the SSR stereoisomer. A.A. Patchett et al., A New Class of Angiotensin-Converting Enzyme Inhibitors, 288 Nature 280 (Nov. 20, 1980), available at J.A. 15475. The Merck article taught how to separate the all-S isomer using standard chromatography techniques.

Both Aventis and its competitor Schering sought to create new ACE inhibitors based on enalapril. Soon after enalapril's introduction, Dr. Elizabeth Smith, a chemist at

Schering, conceived of the structure of ramipril and recorded it in her laboratory notebooks. Ramipril has the same overall structure as enalapril, with one distinction: where ramipril has two linked five-sided carbon rings (a "5,5 fused ring system"), depicted, in the chemical diagrams above, on the left side of the molecule, enalapril has only a single ring. The addition of the second ring gives rise to two more stereocenters than are present in enalapril; thus, ramipril has the same three stereocenters as enalapril, plus two new ones that span the fused ring system and are therefore known as "bridgehead" carbons, for a total of five as discussed above.

Based on the work of Dr. Smith, Schering filed U.S. Patent Application No. 06/199,886 ("the '886 application") on October 23, 1980. Thereafter, the U.S. Patent and Trademark Office ("PTO") granted Schering Patent No. 4,587,258 ("the '258 patent," issued May 6, 1986) and No. 5,348,944 ("the '944 patent," issued Sept. 20, 1994), both claiming priority from the '886 application via a series of continuations and continuations-in-part. The '886 application, the '258 patent, and the '944 patent disclose the structure of ramipril but do not describe how its stereocenters should be configured.

Example 20 of the '886 application discloses a method for making ramipril and is contained in the published specification of the '944 patent. '944 patent, col. 15, ll. 1–15. The title of Example 20 encompasses only eight of the 32 stereoisomers of ramipril, but there is some suggestion in the record that, in fact, Example 20 would have produced only four stereoisomers in practice. Invalidity Opinion at 22–23. The district court described one of the experts testifying on the topic as "somewhat credible" and did not make any explicit findings as to which stereoisomers Example 20 would create. Id. at

23. For purposes of this appeal, it is sufficient to observe that it is uncontested that Example 20 yields a mixture of several, but not all, stereoisomers of ramipril, one of which is the 5(S) form. It appears likely that in some of these stereoisomers, the "bridgehead" carbons are in the R configuration.

In February 1981, Dr. Smith synthesized a mixture of 5(S)-configuration ramipril and its SSSSR stereoisomer, which mixture came to be known as SCH 31925. To make SCH 31925, Smith followed the process disclosed in Example 20, with one "tweak": she used a catalytic hydrogenation step instead of the mercuric acetate oxidation step taught by Example 20. The record is unclear as to why Smith used that step, but there has been no showing that Smith was attempting to select particular stereoisomers. However, the district court found, and Aventis does not dispute on appeal, that SCH 31925—the product of the process as modified by Smith—contains exactly two isomers, the 5(S) and SSSSR forms, and was successfully produced by Dr. Smith. In both the 5(S) and SSSSR forms, the two "bridgehead" carbons are in the S configuration. In light of the teachings of Example 20, Dr. Smith's written laboratory notebooks, and the test results that Dr. Smith obtained within weeks of SCH 31925's synthesis, we see no clear error in the district court's findings that Dr. Smith had conceived of the various stereoisomers and appreciated which of them SCH 31925 contained. See id. at 22–23, 68–69. Moreover, in vivo testing completed by the end of March 1981 confirmed the mixture's therapeutic activity as well as its stereochemistry. We agree with the district court that Dr. Smith did not separate the 5(S) and SSSSR isomers, and there is no evidence that she conceived of a purified formulation containing only 5(S) ramipril. Id. at 69.

In October 1981, Dr. Volker Teetz, an Aventis chemist, also synthesized ramipril. Id. at 23. On November 5, 1981, Aventis filed a German precursor to the application that would become the '722 patent-in-suit. On November 3, 1982, Aventis filed the first in a chain of U.S. patent applications that led to the '722 patent. In all these applications, Aventis claimed the benefit of the German application. There is no dispute that Aventis is entitled to the November 5, 1981 priority date.

On May 6, 1986, Schering's '258 patent issued. Shortly thereafter, Schering granted Aventis a royalty-bearing license under the '258 patent. Around the same time, the PTO declared Interference No. 101,833 between the '258 patent and a pending continuation application belonging to Aventis. The interference settled. Schering agreed to reduce Aventis's royalty payment and to disclaim some of its patent claims. In exchange, Aventis conceded priority as to the primary subject matter of the '258 patent—the structure, production, and therapeutic use of ramipril, without specification of particular stereoisomers. Aventis retained the right to prosecute its application as to the 5(S) stereoisomer of ramipril in formulations "substantially free of other isomers," which it contended (and still contends) represents a separately patentable invention.

The dispute about patent rights having been resolved between Schering and Aventis, Aventis proceeded to seek FDA approval of ramipril (apparently in a substantially pure 5(S) form). On January 28, 1991, the FDA granted approval, and Aventis began to sell ramipril under the name Altace®. Acting as Schering's agent, Aventis sought and obtained an extension of the '258 patent's term on the basis of the period of regulatory review by the FDA.

On October 29, 1991, the '722 patent issued.

C. Procedural History

The ’258 patent expired on January 27, 2005. On March 18, 2005, Lupin filed an ANDA seeking approval for a generic version of ramipril. In response, pursuant to 35 U.S.C. § 271(e)(2)(A), Aventis sued Lupin for infringement, including willful infringement, of the ’722 patent in the United States District Court for the Eastern District of Virginia.

The district court granted Lupin’s Rule 12(c) motion for judgment on the pleadings as to Aventis’s claim for willful infringement and dismissed that claim, leaving only counts alleging non-willful infringement. Aventis Pharma Deutschland GmbH v. King Pharms., Inc., No. 2:05-CV-421 (E.D. Va. Jan. 18, 2006). After construing the claims, see Aventis Pharma Deutschland GmbH v. King Pharms., Inc., No. 2:05-CV-421 (E.D. Va. May 11, 2006), the district court considered the issue of infringement pursuant to motions filed by both sides for summary judgment. The district court declined to grant summary judgment to either party as to literal infringement, finding disputed issues of material fact as to whether Lupin’s formulation of ramipril was “substantially free of other isomers.” Aventis Pharma Deutschland GmbH v. King Pharms., Inc., No. 2:05-CV-421, slip op. at 11–16 (E.D. Va. June 5, 2006). However, the district court granted summary judgment of infringement under the doctrine of equivalents, subject to a subsequent ruling as to the ’722 patent’s validity. Id.

The district court then held a bench trial on validity. During the trial, the district court orally granted Aventis’s motion for judgment as a matter of law that the ’722 patent was not unenforceable for inequitable conduct. On July 17, 2006, the district court issued its opinion on validity, concluding that the ’722 patent was neither anticipated nor

obvious. Invalidity Opinion at 87. Although the district court "reache[d] this decision reluctantly" and observed that "[i]f the standard . . . had been by a preponderance of the evidence rather than by clear and convincing evidence, the Court might have determined this case in Lupin's favor," id. at 1–2, the court concluded that the prior art did not teach ramipril "substantially free of other isomers," nor would a person of ordinary skill in the art "have necessarily been motivated to isolate Ramipril in the 5(S) configuration substantially free of other isomers," id. at 75.

Lupin appeals. Aventis cross-appeals, asserting error in the district court's finding that the filing of an ANDA cannot give rise to willful infringement. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A. The Relevant Prior Art

The record contains a litany of potential prior art references, only some of which are summarized in Part I.B above, and the prosecution histories of both the '722 patent and Schering's ramipril patents are complex. Accordingly, and because Aventis challenges the prior art status of a number of the references that Lupin cites, we begin by identifying and describing the references on which our decision depends and explaining why we consider them to be prior art.

Least controversial are the various references regarding BPP_{5a}, captopril, and enalapril. It is uncontested that these references were publicly disclosed or published well before the development of ramipril and that both Schering's and Aventis's efforts towards developing ramipril were based on this body of earlier knowledge. Notably, all of the stereocenters in the most therapeutically active stereoisomers of these prior art

compounds are in the S configuration, and this fact was taught by, among other references, Merck's enalapril article in Nature.

Unlike these earlier references, however, Aventis challenges the prior art status of the '944 patent.[3] The '944 patent, it observes, is a continuation-in-part of Schering's U.S. Patent Application No. 06/258,484 ("the '484 application"), itself a continuation-in-part of the '886 application. Because Schering had abandoned the '484 application before the '944 patent's filing date, Aventis argues, 35 U.S.C. § 120 bars the '944 patent from benefiting from the earlier '886 filing date. Lupin responds that the PTO cured this defect by reviving the '484 application nunc pro tunc. We need not and do not decide Aventis's challenge on this ground, however, because Aventis presents it for the first time on appeal. In the district court, the '944 patent was relied upon as prior art and its status went unchallenged. Accordingly, the issue is waived. See Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, 1426 (Fed. Cir. 1997). We thus consider the '944 patent entitled to the '886 filing date and treat it as prior art to the '722 patent. The '944 patent discloses Example 20 and also contains the following teaching: "When diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods." '944 patent, col. 10, ll. 28–31.

Finally, we rely, as did the district court, on Dr. Smith's synthesis of SCH 31925, which qualifies as prior art under 35 U.S.C. § 102(g) as of a date no later than the end of March 1981, several months before Aventis's own synthesis of ramipril. See E.I. du

[3] Aventis also challenges the prior art status of the '258 patent on the ground that it is a continuation-in-part containing previously undisclosed new matter. We need not resolve this issue because we do not rely on the '258 patent.

Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1436–37 (Fed. Cir. 1988) (discussing use of § 102(g) prior art in § 103 obviousness determinations). Section 102(g) affords prior art status to an "invention [that] was made in this country by another inventor who had not abandoned, suppressed, or concealed it." 35 U.S.C. § 102(g). Aventis argues that Dr. Smith "abandoned, suppressed, or concealed" SCH 31925, but we see no error in the district court's implicit rejection of this argument. A very similar method to the one Dr. Smith used had already been disclosed in the '886 patent application, the exact method was subsequently disclosed in the '258 patent, and the composition was developed in the course of extensive ongoing research and development and concurrent ongoing patent prosecution. There has been no showing either that Smith "intentionally suppress[ed] or conceal[ed] h[er] invention" or that an "inference of suppression or concealment can be drawn based on an unreasonable delay in making the invention publicly known." Flex-Rest, LLC v. Steelcase, Inc., 455 F.3d 1351, 1358 (Fed. Cir. 2006). Accordingly, SCH 31925—a mixture of 5(S) ramipril with its SSSSR stereoisomer—is part of the prior art.

B. Obviousness of Claims 1 and 2

We turn to the question of obviousness. "Obviousness is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1289 (Fed. Cir. 2006). The key question is whether the 5(S) stereoisomer of ramipril, in a form substantially free of other isomers,[4] would have been obvious over the prior art

[4] We note that the parties dispute the claim construction of "substantially free of other isomers." We need not address this question directly, however, because their dispute centers on how much of another isomer a composition might contain while

listed above to one of ordinary skill in the art at the time of the '722 patent's priority date. See 35 U.S.C. § 103(a). Such a composition is precisely the subject matter of claim 2 of the '722 patent, but the question is dispositive of the obviousness of claim 1 as well, because claim 1 is to a broader genus containing the same subject matter. See, e.g., Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 971 (Fed. Cir. 2001) (noting that a "genus claim limitation is anticipated by, and therefore not patentably distinct from, [a] species claim").

The district court held that Lupin failed to meet its burden of proof by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to purify 5(S) ramipril into a composition substantially free of other isomers. Invalidity Opinion at 74–75. The district court saw this as a close case based principally on the absence of a clear and convincing showing of motivation. Since the date of that decision, however, the Supreme Court decided KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), which counsels against applying the "teaching, suggestion, or motivation" ("TSM") test as a "rigid and mandatory formula[]." See KSR, 127 S. Ct. at 1741. It remains necessary to show "'some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness,'" but such reasoning "need not seek out precise teachings directed to the specific subject matter of the challenged claim." See id. (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)). Requiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is the active

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still remaining "substantially free of other isomers." Whatever the answer to this question might be, it is undisputed that SCH 31925 and the other mixtures of ramipril isomers in the prior art are mixtures that are not substantially free of isomers other than the 5(S) form, whereas the claimed composition of 5(S) ramipril is ipso facto "substantially free" enough.

ingredient is precisely the sort of rigid application of the TSM test that was criticized in KSR.

In the chemical arts, we have long held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., No. 06-1329, slip op. at 9 (Fed. Cir. June 28, 2007) (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)); see also In re Papesch, 315 F.2d 381 (C.C.P.A. 1963). The "reason or motivation" need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship . . . to create an expectation," in light of the totality of the prior art, that the new compound will have "similar properties" to the old. Dillon, 919 F.2d at 692; see also In re Wilder, 563 F.2d 457, 460 (C.C.P.A. 1977) ("[O]ne who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties."). Once such a prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties. Dillon, 919 F.2d at 692.

The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art. Such a purified compound is not always prima facie obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable

weight in itself. However, if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified. See In re May, 574 F.2d 1082, 1090–94 (C.C.P.A. 1978) (holding isolated stereoisomer nonobvious over racemic mixture of stereoisomers, after conceded prima facie showing of obviousness, because isolated stereoisomer was unexpectedly nonaddictive); In re Adamson, 275 F.2d 952, 954–55 (C.C.P.A. 1960) (holding isolated stereoisomer obvious over racemic mixture of stereoisomers, given insufficient showing of any unexpected result); see also In re Merz, 97 F.2d 599, 601 (C.C.P.A. 1938) (holding, prior to the enactment of § 103, that an applicant "is not entitled to a patent on [an] article which after being produced has a greater degree of purity than the product produced by former methods" unless the purification results in "properties and characteristics which were different in kind from those of the known product rather than in degree"). Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art. If it is known how to perform such an isolation, doing so "is likely the product not of innovation but of ordinary skill and common sense." KSR, 127 S. Ct. at 1742.

The record suggests that when Dr. Smith synthesized SCH 31925, she understood that the 5(S) form of ramipril was the mixture's therapeutically active ingredient. Even if she did not, however, the prior art provides a sufficient reason to

look to the 5(S) configuration. The SCH 31925 composition contained only the 5(S) and SSSSR stereoisomers of ramipril. Importantly, these forms differ by the configuration of only one carbon atom, and that atom is not one of the "bridgehead" carbons. Rather, that carbon atom is in the part of the ramipril molecule that is common to the enalapril molecule. In enalapril, as in captopril and BPP_{5a} before it, all of the stereocenters are in the S configuration; the Merck article taught that the SSS configuration of enalapril is 700 times as potent as the SSR form. The close structural analogy between 5(S) and SSSSR ramipril and SSS and SSR enalapril would have led a person of ordinary skill to expect 5(S) and SSSSR ramipril to differ similarly in potency. Moreover, the '944 patent specifically taught that stereoisomers of ramipril "can be separated by conventional chromatographic or fractional crystallization methods." '944 patent, col. 10, ll. 28–31. Aventis's protestations notwithstanding, there is no evidence that separating 5(S) and SSSSR ramipril was outside the capability of an ordinarily skilled artisan.

Aventis attempts to rebut this prima facie case of obviousness by arguing that purified 5(S) ramipril exhibited unexpected results in the form of increased potency. In support, Aventis points to the district court's finding that 5(S) ramipril is 18 times as potent as the next most potent isomer, the RRSSS form. Invalidity Opinion at 44. Aventis is correct that, on the basis of the record, the RRSSS and 5(S) forms might have been expected to have comparable potencies; both of them have only S-configured stereocenters in the part of the ramipril molecule that is common to enalapril, as the R stereocenters in the RRSSS form are the "bridgehead" carbons. This, however, is the wrong comparison. The prior art supporting prima facie obviousness included the SCH 31925 mixture, and so Aventis must show that 5(S) ramipril had

unexpected results not over all of its stereoisomers, but over that mixture, which did not contain the RRSSS form. And the potency of pure 5(S) ramipril is precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers. All evidence suggests, and the district court found, that potency varies with the absolute amount of the 5(S) isomer in a mixture. Invalidity Opinion at 37. That is, a 30 milligram dose of a mixture that is 1/3 5(S) ramipril has the same effectiveness as a 10 milligram dose of pure 5(S) ramipril. Id. Aventis has thus failed to show unexpected results that would tend to rebut a prima facie case of obviousness. See Pfizer v. Apotex, 480 F.3d 1348, 1368–69 (Fed. Cir. 2007) (holding obvious a patent claim to amlodipine besylate over prior art disclosing the small genus of pharmaceutically acceptable amlodipine salts, where there was an insufficient showing that the properties of amlodipine besylate, purportedly superior for the purpose of mass-manufacturing tablets, were unexpectedly superior to other obvious-to-try salts); cf. Forest Labs., Inc. v. Ivax Pharms., Inc., No. 07-1059, slip op. at 10–11 (Fed. Cir. Sept. 5, 2007) (holding that prima facie obviousness of a claim to a particular stereoisomer over a racemic mixture was rebutted where the particular stereoisomer showed unexpected benefits and evidence indicated that the isomers would have been difficult for a person of ordinary skill in the art to separate).

In sum, we hold that claims 1 and 2 of the ’722 patent, which cover the 5(S) stereoisomer of ramipril in a composition substantially free of other isomers, are invalid under 35 U.S.C. § 103 over the SCH 31925 mixture, the ’944 patent, and the enalapril references in the prior art.

C. Obviousness of Claims 4 and 5

Two asserted claims of the ’722 patent remain for discussion. Claim 4 addresses a “hypotensive composition” of the compound in claim 1 “comprising a hypotensively effective amount” of the compound “and a pharmaceutically acceptable excipient therefor.” Claim 5 addresses a “method for reducing blood pressure” by administering the compound of claim 1. The parties argue this case by discussing the invalidity of the ’722 patent as a whole, but “we must evaluate obviousness on a claim-by-claim basis.” DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1372 (2006). However, the parties do not challenge the district court’s observation that “all the claims rise or fall with the validity of claim 1,” Invalidity Opinion at 17, and with good reason. The added limitations of claims 4 and 5 appear almost verbatim in virtually all the prior art patents, including the ’944 patent and its parent ’886 application. E.g., ’944 patent, claims 3–4, col. 36, ll. 43–52. The prior art thus reveals that it was well understood by ordinarily skilled artisans that ACE inhibitors were to be used in the manner these claims describe. Accordingly, we hold that claims 4 and 5 of the ’722 patent are also invalid as obvious.

III. CONCLUSION

Having concluded that all asserted claims of the ’722 patent are invalid as obvious, we need not reach Lupin’s remaining arguments in favor of reversal. Likewise, Aventis’s cross-appeal is moot. Because Lupin is entitled to entry of judgment in its favor, the judgment of the district court is

REVERSED.